

Case Report

A Paternally Inherited *BRCA1* Mutation Associated with an Unusual Aggressive Clinical Phenotype

Florentia Fostira,¹ Nikolaos Tsoukalas,² Irene Konstantopoulou,¹ Vassilios Georgoulas,³ Charalambos Christophyllakis,² and Drakoulis Yannoukakos²

¹ Molecular Diagnostics Laboratory, INRASTES, NCSR Demokritos, 15310 Athens, Greece

² Medical Oncology Unit, "401" General Military Hospital, 11525 Athens, Greece

³ Department of Medical Oncology, University General Hospital of Heraklion, 71110 Crete, Greece

Correspondence should be addressed to Florentia Fostira; florentia_fostira@hotmail.com

Received 23 November 2013; Accepted 24 December 2013; Published 10 February 2014

Academic Editors: D. J. Bunyan, S. Ennis, F.-C. Hsu, and M. G. Kibriya

Copyright © 2014 Florentia Fostira et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

This report highlights the necessity of genetic testing, at least for *BRCA1* mutations, of young females diagnosed with triple negative breast cancer, even in the absence of or limited family history. A 34-year-old female with a locally advanced, triple negative tumour, which perforated the skin, is described. At the time of diagnosis, the patient had already multiple lung metastases and although chemotherapy was started immediately, she died with rapid systemic disease progression. The patient was found to carry the *BRCA1* p.E1060X mutation, which is located on exon 11 of the gene. The high penetrance of *BRCA1* gene is not represented in the patient's family, since the mutation was paternally inherited. It is evident that females belonging to small families, along with paternal inheritance of pathogenic *BRCA* mutations that predispose for breast cancer, in most cases will probably be genetically tested only after being diagnosed with cancer.

1. Introduction

BRCA1 and *BRCA2* genetic testing has been available in the clinic at least for the past decade, allowing the characterization of people that face an increased breast and ovarian cancer risk. Although the selection criteria for genetic testing are quite established, many times the small size of the family or the paternal inheritance of the pathogenic *BRCA* mutation can be misleading when referring patients. Therefore, loss-of-function mutations can be genetically transmitted from male *BRCA* mutation carriers, who can be in many cases cancer-free, to their daughters, who will have a lifetime breast cancer risk that can be as high as 84% [1–3]. Estimated lifetime breast cancer risk for male *BRCA2* carriers is approximately 8% [4], while there is high relative risk for pancreatic and prostate cancer, when compared to the general population [5]. On the contrary, relative and cumulative cancer risks are much lower in male *BRCA1* carriers [6]. Since our current knowledge is advanced on understanding the cancer predisposition of mutation carriers, it seems rather important to successfully

identify these individuals in order to offer appropriate clinical management.

2. Case Report

A 34-year-old premenopausal female with a locally advanced tumour presented as a dirty ulcer, perforating the skin, in her right breast is described. Biopsies of the damaged tissue showed an invasive, grade III ductal carcinoma, with areas of papillary shaping, areas of necrosis, and invasion of the skin. The breast tumour was classified as triple negative, since there was a lack of estrogen and progesterone receptor expression and absence of HER2 oncoprotein after immunohistochemical staining. Staging revealed multiple lung metastases and enlargement of right axillary lymph nodes. Consequently, she was diagnosed with a stage IV infiltrating ductal cancer in her right breast which was triple negative and grade III.

The patient was started on first line chemotherapy with the regimen carboplatin 2AUC and paclitaxel 80 mg/m²

weekly plus bevacizumab 10 mg/Kgr on days 1 and 15. Initially she had a partial response to this treatment. However, her disease relapsed and she started on second line chemotherapy with the regimen docetaxel 75 mg/m², adriamycin 60 mg/m², and cytoxan 600 mg/m² every 21 days. She received only two cycles of this chemotherapy because she was admitted to hospital due to multiple brain metastases. She was administered whole brain radiotherapy with minimal improvement of her clinical symptoms. Taking into account the triple negative, along with the *BRCA1* mutation status, the patient was considered as a candidate for entering a clinical trial with PARP inhibitors. Unfortunately, due to a rapid systemic disease progression the patient finally passed away a month later and therefore did not receive any further treatment.

The proband had limited family history of breast or ovarian cancer. It is noteworthy that the family was rather small (Figure 1). Her grandmother from her father's side was diagnosed with breast cancer and died at her early fifties. The other reported cancer in her first degree relatives is the prostate cancer diagnosed in her father when he was 72. He underwent prostatectomy for prostate cancer, due to his elevated PSA value (7 ng/mL). The histology report revealed the existence of a low differentiated adenocarcinoma of the prostate gland with Gleason's pattern 7 (4+3). Also there were some areas with high grade prostatic intraepithelial neoplasia (PIN). The stage of the disease was T3bN0M0. Consequently, he was diagnosed with a high risk prostate cancer based on T3b. Initially, he received radiotherapy and hormonal therapy with LHRH analogue and specifically triptoreline and antiandrogen (bicalutamide).

Many research groups have reported that *BRCA1* and *BRCA2* mutation carriers are more likely to develop a more aggressive prostate cancer phenotype, generally associated with a higher probability of nodal involvement, distant metastasis, and low grade tumours [7, 8]. This observation is consistent with this case.

Due to the early age of breast cancer diagnosis, along with the distinct immunophenotype, the patient fulfilled the updated NCCN guidelines (<http://www.nccn.org/>) and was therefore tested for deleterious mutations in *BRCA1* and *BRCA2* genes. The direct relationship between *BRCA1* mutations and triple negative breast cancer has been widely assessed in Greek patients [9]. Direct Sanger sequencing revealed the nonsense mutation p.E1060X (c.3178G>T), which is located on exon 11 of the *BRCA1* gene. This is a rare, to the Greek population, mutation. The proband's father was tested to be the mutation carrier, while the proband's sister (cancer free at the age of 45) did not carry the damaging allele.

3. Discussion

This case report highlights the necessity of genetic testing even when family history is not prominent, at least for *BRCA1* mutations, of young females diagnosed with triple negative breast cancer. Individuals belonging in small families in combination with paternal inheritance of pathogenic mutations can remain undiagnosed. Some recent research studies indicate that females with paternally inherited mutations

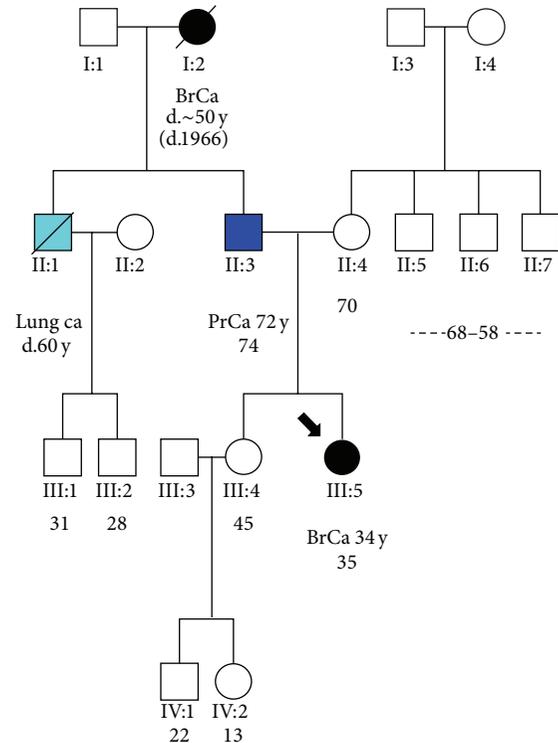


FIGURE 1: Pedigree of the family where the *BRCA1* mutation p.E1060X (c.3178G>T) was identified. The proband is highlighted by the arrow.

in *BRCA* gene mutations develop breast cancer at younger age when compared to women who inherit the gene mutations from their mothers. This can be partially explained by different imprinting patterns in maternal and paternal chromosomes and more specifically in the *BRCA1* or *BRCA2* locus [10].

We report this case as it highlights the importance of careful selection of individuals for genetic testing. The necessity for identification of mutation carriers is enlarged since there are promising, targeted therapies for *BRCA1* carriers, such as PARP inhibitors.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' Contribution

Florentia Fostira and Nikolaos Tsoukalas equally contributed to this work.

References

- [1] D. Ford, D. F. Easton, M. Stratton et al., "Genetic heterogeneity and penetrance analysis of the *BRCA1* and *BRCA2* genes in breast cancer families," *The American Journal of Human Genetics*, vol. 62, no. 3, pp. 676–689, 1998.

- [2] A. Antoniou, P. D. Pharoah, S. Narod et al., "Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies," *The American Journal of Human Genetics*, vol. 72, no. 5, pp. 1117–1130, 2003.
- [3] M.-C. King, J. H. Marks, and J. B. Mandell, "Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2," *Science*, vol. 302, no. 5645, pp. 643–646, 2003.
- [4] D. G. Evans, M. Ahmed, S. Bayliss, E. Howard, F. Lalloo, and A. Wallace, "BRCA1, BRCA2 and CHEK2 c.1100 delC mutations in patients with double primaries of the breasts and/or ovaries," *Journal of Medical Genetics*, vol. 47, no. 8, pp. 561–566, 2010.
- [5] A. Liede, B. Y. Karlan, and S. A. Narod, "Cancer risks for male carriers of germline mutations in BRCA1 or BRCA2: a review of the literature," *Journal of Clinical Oncology*, vol. 22, no. 4, pp. 735–742, 2004.
- [6] Y. C. Tai, S. Domchek, G. Parmigiani, and S. Chen, "Breast cancer risk among male BRCA1 and BRCA2 mutation carriers," *Journal of the National Cancer Institute*, vol. 99, no. 23, pp. 1811–1814, 2007.
- [7] E. Castro, C. Goh, D. Olmos et al., "Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer," *Journal of Clinical Oncology*, vol. 31, no. 14, pp. 1748–1757, 2013.
- [8] A. V. Mitra, E. K. Bancroft, Y. Barbachano et al., "Targeted prostate cancer screening in men with mutations in BRCA1 and BRCA2 detects aggressive prostate cancer: preliminary analysis of the results of the IMPACT study," *BJU International*, vol. 107, no. 1, pp. 28–39, 2011.
- [9] F. Fostira, M. Tsitlaidou, C. Papadimitriou et al., "Prevalence of BRCA1 mutations among 403 women with triple-negative breast cancer: implications for genetic screening selection criteria: a Hellenic Cooperative Oncology Group Study," *Breast Cancer Research and Treatment*, vol. 134, no. 1, pp. 353–362, 2012.
- [10] N. Senst, M. Llacuachaqui, J. Lubinski et al., "Parental origin of mutation and the risk of breast cancer in a prospective study of women with a BRCA1 or BRCA2 mutation," *Clinical Genetics*, vol. 84, no. 1, pp. 43–46, 2013.